Dietary Fat, Fat Subtypes, and Breast Cancer in Postmenopausal Women: a Prospective Cohort Study

Ellen Velie, Martin Kulldorff, Catherine Schairer, Gladys Block, Demetrius Albanes, Arthur Schatzkin

Background: **The intake of total dietary fat and of certain fat subtypes has been shown to be strongly associated with breast cancer in international comparisons and in animal experiments. However, observational epidemiologic studies have generally reported either weak positive or no associations. To extend the prospective epidemiologic evidence on this question, we examined the association between adult dietary intake of fat, fat subtypes, and breast cancer in a large, prospective cohort of postmenopausal women.** ***Methods:*** **Participants were selected from a national breast cancer mammography screening program conducted from 1973 through 1981 at 29 centers throughout the United States. From 1987 through 1989, 40 022 postmenopausal women satisfactorily completed a mailed, self-administered questionnaire that included a 60-item National Cancer Institute/Block food-frequency questionnaire. Women were then followed for an average of 5.3 years; 996 women developed breast cancer. Risk was assessed by use of Cox proportional hazard regression, with age as the underlying time metric. All statistical tests were two-sided.** ***Results:*** **Compared with women in the lowest quintile (Q1) of percentage of energy from total fat, the adjusted risk ratio (RR) and 95% confidence interval (CI) for women in the highest quintile (Q5) was 1.07 (95% CI = 0.86–1.32). In analyses stratified by history of benign breast disease (BBD), a positive association was observed among only women with no history of BBD ($RR_{Q5\ versus\ Q1}$ = 2.20; 95% CI = 1.41–3.42; test for trend, *P* = .0003). The increased risk in these women appeared to be attributable to unsaturated fat intake and oleic acid in particular.** ***Conclusions:*** **In this study, there was no overall association between fat intake during adulthood and breast cancer risk; however, among women with no history of BBD, there appeared to be a positive association between total and unsaturated fat intake and breast cancer risk. [J Natl Cancer Inst 2000;92:833–9]**

Breast cancer is among the most prevalent types of cancer in women, both worldwide and within the United States *(1)*. In the United States, the incidence of breast cancer was 110 per 100 000 women in 1996 *(2)*, and in countries with traditionally lower incidences, substantial increases have occurred in recent decades *(1)*. Because few modifiable risk factors for the disease have been identified *(3)*, potential dietary associations are of great interest.

The association between fat intake and breast cancer has generated considerable debate *(4,5)*. Per capita total fat, saturated fat, and monounsaturated fat supplies were shown to be strongly correlated with breast cancer incidence between countries and within countries over time *(6–8)*. Populations migrating from areas with low-fat diets to those with high-fat diets acquire the destination country's incidence and mortality within one generation *(6,9)* or even decades *(10,11)*. The latter suggests that adult exposures influence breast cancer risk. Animal experiments suggest that total and polyunsaturated fat intake (linoleic acid, in particular) promotes mammary tumorigenesis *(12,13)*, whereas the effects of saturated fat and monounsaturated fat (oleic acid, in particular) are inconsistent *(12,14,15)*.

Evidence from observational epidemiologic studies is conflicting. Most case–control studies have shown a modest increased risk associated with increased intake of total fat and various fat subtypes during adulthood and breast cancer *(16)*. Prospective cohort studies *(17–23)*, however, have provided little support for the dietary fat–breast cancer hypothesis for either total fat or fat subtypes *(24–26)*.

We had the opportunity to investigate the association between total dietary fat and fat subtype intake and breast cancer risk in a large, prospective cohort study of postmenopausal women.

Subjects and Methods

Study Population

Subjects are participants in the Breast Cancer Detection Demonstration Project (BCDDP) Follow-up Cohort Study. They were selected from past participants in the BCDDP, a breast cancer-screening program conducted from 1973 through 1981 in which more than 280 000 women received up to five annual breast cancer screenings at 29 centers throughout the United States. Beginning in 1979, the National Cancer Institute (Bethesda, MD) began the BCDDP Follow-up Cohort Study on a subset of the BCDDP participants (n = 64 182).

Women were selected for follow-up study on the basis of their status at their last screening visit: diagnosis of breast cancer (n = 4275), nonmalignant or benign breast disease (BBD) determined by biopsy or breast surgery (n = 25 114), or recommended for biopsy or breast surgery but did not have the surgery performed (n = 9628). In addition, a sample of women identified by screening to have no evidence of breast disease was included (n = 25 165). The latter group was matched to those with breast cancer and BBD on age and time at entry to the BCDDP program, race, center, and length of participation in the program. The BCDDP Follow-up Cohort Study was approved by the Institutional Review Board at the National Cancer Institute, and written informed consent was obtained from all participants.

Data were collected in three phases. In phase 1, a baseline interview and up to six annual telephone interviews were administered (from 1979 through 1986); in phase 2, a follow-up questionnaire was mailed to the subjects (from 1987 through 1989); and in phase 3, a second follow-up questionnaire was mailed to the subjects (from 1993 through 1995). For all nonresponders to the mailed questionnaire, repeated attempts were made to conduct follow-up interviews by telephone. Extensive efforts were made throughout the study to locate women lost to follow-up, including attempted tracing through the National Center for Health Statistics National Death Index through 1993.

Exposures and Covariates

Information about dietary intake and vitamin supplement use, alcohol intake, self-reported height and weight, and tobacco use was obtained in the second-phase mailed questionnaire (from 1987 through 1989). At the baseline interview (from 1979 through 1986), information was obtained about family history of breast cancer in a first-degree relative, history of biopsies for BBD, use of female hormones or oral contraceptives, age at menarche, parity, age

Affiliation of authors: E. Velie, A. Schatzkin (Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics), C. Schairer (Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics), D. Albanes (Cancer Prevention Studies Branch, Division of Clinical Sciences), National Cancer Institute, Bethesda, MD; M. Kulldorff, Division of Biostatistics, Department of Community Medicine and Health Care, University of Connecticut School of Medicine, Farmington; G. Block, Department of Public Health Nutrition, University of California, Berkeley.

Correspondence to: Ellen Velie, Ph.D., National Institutes of Health, 6120 Executive Blvd., MSC 7232, EPS, Rm. 7026, Bethesda, MD 20892 (e-mail: veliee@mail. nih.gov).

See "Notes" following "References."

at first live birth, date of cessation of menstrual period, reason for cessation of menstrual periods if no period was reported within the 3 months prior to the interview, and any surgical procedures on the breast. Annual telephone interviews and mailed follow-up questionnaires were used to update this information. Educational level was obtained at the first screening visit. Body mass index (BMI) was defined as weight in kilograms divided by squared height in meters. History of BBD was defined at the time of the second-phase interview as positive if a woman had ever had a biopsy that indicated benign rather than malignant breast disease (22 287 [84.7%] of 26 315 women with BBD) or was recommended for a biopsy but it had not yet been conducted (4028 [15.3%] of women with BBD). For most women, BBD information was obtained from medical record reports (87%). For women having a first biopsy prior to inclusion in the study, BBD information was based on self-report (13%).

Dietary Assessment

Average daily dietary intake information was assessed by use of the Block/National Cancer Institute 60-item food-frequency questionnaire *(27–29)*. Women were asked to report their usual food intake during the previous year. The questionnaire has been described in detail, and its validity and reproducibility have been reported elsewhere *(29–31)*. With software developed for the survey instrument, the frequency of consumption of each food was multiplied by the nutrient content of reported portion sizes to generate average daily intakes of nutrients and energy. Frequency of servings of fruits and vegetables were also calculated *(27)*. Questionnaires with reported caloric intakes of fewer than 400 kcals per day or greater than or equal to 3800 kcals per day, as well as those with 30 or more skipped food items, were considered to be inaccurate and were excluded from analyses (n = 5051).

The primary exposures of interest were intake of total fat and fat subtypes. Among the foods asked about on the 60-item food-frequency dietary intake instrument, the top dietary sources and percent contribution to total fat in this analytic cohort were as follows: mayonnaise and salad dressing (13.2%); margarine (10.5%); cheese and cheese spread (6.4%); salty snacks (chips and popcorn) (5.1%); 2% milk (4.4%); doughnuts, cookies, and cake (4.2%); ice cream (3.9%); hamburger, beef burrito, and meatloaf (3.8%); eggs (3.6%); and peanuts and peanut butter (3.2%). Among fat types, most of these same foods were major contributors, with a shift in the order of contribution for each fat type. The top two contributors for each fat subtype (although they represent only a small percentage of total intake) were as follows: for saturated fat (cheese and cheese spread [11.9%] and 2% milk [8.7%]); for linoleic acid (mayonnaise and salad dressings [32.7%] and margarine [16.2%]); and for oleic acid (margarine [13.2%] and mayonnaise and salad dressings [8.7%]).

Analytic Cohort

Of the 64 182 women selected for participation in the follow-up study, 61 433 (96%) completed the baseline interview and were available for study. Of these women, those who were premenopausal at the third-phase questionnaire (from 1993 through 1995) (n = 1370) or who had been diagnosed with breast cancer prior to or at the time of completion of the second-phase questionnaire (from 1987 through 1989) (n = 6431) were considered to be ineligible and excluded from analyses. Menopause was defined as not experiencing a menstrual period during the previous 3 months. Women reporting surgical menopause without removal of both ovaries were considered to be menopausal when they reached 52.75 years of age (the median age at natural menopause in this cohort) or the age at hysterectomy, whichever came last (n = 649).

Of the remaining 53 632 eligible women, women were excluded from analyses consecutively for the following reasons: did not complete second-phase questionnaire (n = 7583); unknown or missing menopausal data (n = 476); completed dietary questionnaire considered to be inaccurate (n = 5051); inappropriate start and exit dates (n = 157); and missing covariate information for parity, age at 1st birth, and educational level (n = 343). Missing information for other covariates was either imputed based on the mean value for the cohort or, where noted, included as "don't know" in multivariate analyses. At the administration of the second-phase questionnaire, 92% of the analytic cohort were postmenopausal and 8% became menopausal between the second and third phase of the study. The final analytic cohort included 40 022 women; a total of 26 315 (66%) of them were considered to have a history of BBD, and 13 707 (34%) were considered to have no history of BBD.

Case Identification

Breast cancer cases included in these analyses were identified subsequent to the second-phase questionnaire. Breast cancer status was obtained from self-report, from reports of breast cancer on death certificates, and from relatives. Of the 996 postmenopausal women who developed breast cancer in the analytic cohort, 80% were confirmed by pathology reports. Because the accuracy of reporting was high among those with pathology reports (97% were confirmed as cancers), cancers without pathology reports (n = 204) were included in the analyses. A total of 838 of these cases were considered to be invasive breast cancer, and 158 were *in situ;* cases without pathology reports were considered to be invasive.

Statistical Analysis

Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated by use of Cox proportional hazards regression, with age as the underlying time metric. All tests of significance were two-sided, and all *P* values were calculated by use of the Wald test. Subjects were considered to have entered the cohort at their second-phase interview or date of menopause, whichever came later, and to have exited the study at their diagnosis of breast cancer, death from other causes, last contact, date of bilateral prophylactic mastectomy, or return of the follow-up questionnaire. Ninety percent of the women (35 328 of 40 002) in this analytic cohort were followed through the third phase of the study (from 1993 through 1995).

RRs associated with usual daily intakes of percentage of energy from different dietary components were examined on the basis of quintiles defined for the entire population and as continuous variables. Tests for linear trend were calculated by use of continuous variables modeled as linear terms. Mean intakes of dietary variables with both equal and unequal variances were also compared by use of Student's *t* tests.

All analyses were adjusted for total energy intake. We used four different energy-adjustment methods and report results from the multivariate nutrient density method only, since few differences in associations were observed between methods *(32,33)*. With the multivariate nutrient-density method, the percent of energy from each fat type of interest and total energy intake are included in the analyses. In our study, the quadratic term for energy was statistically significant when adjusted for the percentage of energy from total fat and from all other covariates ($P = .04$). Therefore, to adequately adjust for energy intake, we included the quadratic term in all analyses.

We examined individual fat subtypes after adjustment for other fat subtypes in the analyses. Thus, we included in the multivariate analyses all of the fat subtypes simultaneously, in addition to total energy. Risk estimates associated with each fat type can be interpreted as the effect of the substitution of a percentage of energy from each particular fat type for an equal percentage of energy from nonfat sources of energy only (i.e., protein and carbohydrate). We examined each fat type modeled both in quintiles, with the lowest quintile as the referent, and as a continuous factor. For continuous factors, the risk estimates represent the effect of a five-percentage unit change in energy from each fat type.

In addition to total fat, fat subtypes, and energy, we included in multivariate analyses the following established and suspected risk factors for breast cancer: total energy (quadratic), BMI (quadratic), height (linear), first-degree family history of breast cancer (yes, no, or don't know), parity (yes or no), parity (linear), age at first birth (linear), educational level (less than a high school graduate, high school graduate, some college education, or college graduate), age at menarche (linear), BBD (yes or no), alcohol use (yes or no), and alcohol use (linear). We also examined the effect of the number of weekly servings of fruits and vegetables consumed (linear) and the use of exogenous hormones in the year prior to interview (yes or no) on adjusted estimates.

We examined the association between fat and fat subtypes and breast cancer within strata of history of BBD (yes or no), family history of breast cancer (yes, no, or not sure), BMI (<21, 21–28, and >29 kg/m^2), and alcohol intake (nondrinkers, 1–13 or >13 g/day). We also examined interaction terms from multivariate models for percentage of energy from total fat and each of these factors.

RESULTS

Study participants (n = 40 022) averaged 62 years of age (range, 42–91 years) at the start of follow-up and were followed an average of 5.3 years (range, 0.8–8.2 years). Participants were predominantly white (n = 35 477; 89%) and parous (n = 34 753; 87%) and had a history of BBD (n = 26 315; 66%). Forty-six percent (n = 18 371) had at least some

college education or a higher degree, and 21% (n = 8295) had a first-degree family history of breast cancer.

Average daily intakes and quintile median values for percentage of energy from total fat, fat subtypes, protein, and carbohydrate, as well as total energy intake, are shown in Table 1.

In analysis of covariates, total fat intake as a percentage of energy decreased with increasing educational level, alcohol intake, and fruit and vegetable intake. It increased with increasing parity, energy intake, and BMI (data not shown). Similar patterns were observed for saturated fat, unsaturated fat, oleic acid, and linoleic acid. In adjusted analyses, increased breast cancer risk was associated with increased educational level, age at first birth, BMI, height, alcohol intake, and decreased age at menarche and parity, as well as a history of BBD, and a family history of breast cancer (data not shown).

As shown in Table 2, percentage of energy from total fat intake was not statistically significantly associated with breast cancer risk ($RR_{Q5\ versus\ Q1}$ = 1.07 [95% CI = 0.86–1.32]; test for trend, P = .51) nor was protein, carbohydrate, or total energy intake. Results were similar when we adjusted for energy intake by use of three other techniques and when we removed energy intake, BMI, and BBD from the model. The addition of servings of fruits and vegetables and recent exogenous hormone use to the model as potential confounders, as well as the removal of women with *in situ* breast cancer from analyses, also had little effect on results.

Table 2 also presents the adjusted RRs associated with quintiles of percentage of energy from fat subtypes. When all of the fat subtypes were included in analyses simultaneously, no statistically significant association between saturated fat, unsaturated fat, oleic acid, linoleic acid, and breast cancer risk was observed.

We hypothesized that a real association between dietary fat intake and breast cancer risk may be attenuated in women with a history of BBD because they are at increased risk of breast cancer and may have changed their diet toward lower fat intake or recalled their diet less accurately as a result of the diagnosis. Consistent with this hypothesis, in the subset of women with a positive history of BBD, we observed no association between total fat intake and breast cancer risk (compared with the 1st quintile [Q1] of intake, RR_{Q2} = 1.1 [95% CI = 0.9–1.3], RR_{Q3}

Table 2. Adjusted risk ratio (RR) of breast cancer by quintiles of percentage energy from fat and fat subtypes, protein, carbohydrates, and energy among 40 022 postmenopausal women in the Breast Cancer Detection Demonstration Project Follow-up Cohort Study (from 1979 through 1995)

Nutrient	Quintile (Q) of intake, % energy or kcals/day					*P* test for trend*
	Q1	Q2	Q3	Q4	Q5	
Total fat, % energy†						
No. of cases	188	218	197	211	182	.51
RR	1.0	1.18	1.08	1.18	1.07	
95% CI		0.97–1.43	0.88–1.32	0.97–1.45	0.86–1.32	
Saturated fat, % energy†,‡						
No. of cases	179	209	228	200	180	.67
RR	1.0	1.20	1.34	1.20	1.12	
95% CI		0.97–1.48	1.07–1.66	0.95–1.51	0.87–1.45	
Unsaturated fat, % energy†,‡						
No. of cases	192	219	181	209	195	.35
RR	1.0	1.17	0.97	1.16	1.13	
95% CI		0.95–1.43	0.78–1.21	0.92–1.46	0.88–1.45	
Oleic acid, % energy†,‡						
No. of cases	191	220	203	210	172	.92
RR	1.0	1.13	1.02	1.07	0.88	
95% CI		0.91–1.41	0.80–1.32	0.80–1.43	0.62–1.25	
Linoleic acid, % energy†,‡						
No. of cases	195	209	190	207	195	.44
RR	1.0	1.08	0.98	1.08	1.05	
95% CI		0.89–1.33	0.79–1.22	0.86–1.35	0.82–1.34	
Protein, % energy†						
No. of cases	192	210	215	200	179	.28
RR	1.0	1.08	1.12	1.04	0.91	
95% CI		0.89–1.32	0.92–1.36	0.85–1.28	0.74–1.13	
Carbohydrates, % energy†						
No. of cases	199	198	197	219	183	.53
RR	1.0	1.00	0.98	1.08	0.91	
95% CI		0.82–1.22	0.80–1.20	0.88–1.32	0.73–1.12	
Energy, kcals§						
No. of cases	183	183	234	209	187	.39
RR	1.0	0.96	1.21	1.05	0.94	
95% CI		0.78–1.18	0.99–1.47	0.86–1.29	0.77–1.16	

*P value (Wald test) for continuous linear term.

†Adjusted for total energy, body mass index, height, family history of breast cancer, parity, age at first birth, educational level, alcohol use, age at menarche, and history of benign breast disease. RR = adjusted risk ratio; CI = confidence interval.

‡Mutually adjusted for other fat subtypes.

§Adjusted for all above factors except energy, saturated fat, and unsaturated fats.

Table 1. Means and distributions of daily intake of total energy and percentage of energy from total fat, fat subtypes, protein, and carbohydrates among 40 022 postmenopausal women participants in the Breast Cancer Detection Demonstration Project Follow-up Cohort Study (from 1979 through 1995)

Nutrient	Mean	±SD*	Percentile				
			10th	30th	50th	70th	90th
Total fat, % energy	35.0	8.5	23.9	30.8	35.2	39.5	45.4
Saturated fat, % energy	11.5	3.4	7.1	9.7	11.5	13.3	15.7
Unsaturated fat, % energy	23.5	5.9	16.1	20.4	23.4	26.3	30.6
Linoleic acid, % energy	7.3	3.2	3.7	5.5	6.9	8.5	11.2
Oleic acid, % energy	12.0	3.2	7.9	10.4	12.1	13.7	16.0
Other unsaturated fat, % energy	4.1	1.2	2.8	3.6	4.1	4.6	5.5
Protein, % energy	17.9	3.7	13.6	16.0	17.7	19.5	22.5
Carbohydrates, % energy	46.5	9.3	35.3	41.7	46.2	48.4	58.3
Total energy, kcals	1269.7	525.3	699.8	959.9	1175.7	1440.0	1936.8

*SD = standard deviation.

= 1.0 [95% CI = 0.8–1.2], RR_{Q4} = 1.0 [95% CI = 0.8–1.3], and RR_{Q5} = 0.8 [95% CI = 0.7–1.1]; test for trend, P = .20). In women with no history of BBD, however, we observed a statistically significant direct association between total fat intake and breast cancer risk (test for linear trend, P = .0003) (Table 3). A test for interaction between percentage of energy from total fat and history of BBD was significant (P = .0007).

On the other hand, among strata of family history of breast cancer, BMI, and alcohol intake, there was no association between total fat intake and breast cancer. Moreover, there was no association between the cross-products of low- and high-fat and low- and high-fruit and vegetable intake and breast cancer.

Table 3 also shows that, in the subset of women with no history of BBD, the statistically significant increased risk associated with total fat intake was attributable to unsaturated fat ($RR_{Q5\ versus\ Q1}$ = 2.64; 95% CI = 1.56–4.44); test for trend, P = .0006). When unsaturated fat intake was divided into its constituents, oleic acid, linoleic acid, and other unsaturated fats, the greatest increased risk was associated with oleic acid intake ($RR_{Q5\ versus\ Q1}$ = 1.82; 95% CI = 0.89–3.71; test for trend, P = .03). Increased carbohydrate intake was also associated with decreased breast cancer risk in these women ($RR_{Q5\ versus\ Q1}$ = 0.51; 95% CI = 0.34–0.77; test for trend, P = .002). Because increased carbohydrate intake is associated with decreased fat intake when energy intake is held constant, the inverse relation between carbohydrate intake and breast cancer may reflect the direct relation between fat and breast cancer.

To compare risk estimates from each fat type, in the subset of women with no history of BBD, we included in the analyses each type as a continuous factor (Fig. 1) *(34)*. Risk estimates represent a five-percentage unit change in energy from each fat subtype. Model 1 includes the percentage of energy from total fat and all other covariates (RR = 1.15; 95% CI = 1.07–1.24; test for trend, P = .0003). Model 2 incorporates the two components of total fat, saturated and unsaturated, simultaneously in the analyses. Only the risk associated with unsaturated fat was statistically significantly elevated (RR = 1.25; 95% CI = 1.10–1.41; test for trend, P = .0006). Model 3 further divides unsaturated fat into oleic acid, linoleic acid, and all other unsaturated fats and also includes saturated fat simultaneously in the analyses. Here, only the risk associated with oleic acid was statistically significant (RR = 1.53; 95% CI = 1.05–2.22; test for trend, P = .03).

We examined several potential explanations for the different associations between fat intake and breast cancer in women with and without a history of BBD. Underlying dietary food-item sources of fat types were similar in both groups of women. Women with a history of BBD did, however, have a slightly lower (mean ± standard deviation) intake of percentage of calories from total fat (34.93 ± 8.5 versus 35.10 ± 8.6) (P = .06), saturated fat (11.47 ± 3.4 versus 11.57 ± 3.4) (P = .005), and grams of alcohol (3.84 ± 9.8 versus 4.07 ± 10.5) (P = .03) and a slightly higher mean intake of fiber (11.54 ± 6.4 versus 11.40 ± 6.1) (P = .03). Multivariate diagnostic procedures to remove influential, extreme outlier data points did not alter the positive association observed. Adjustment for margarine intake (one of the main contributors to both oleic and linoleic acid intake) did not alter the association. Also, the association persisted after removing overweight women and women who drank one drink or more per day from analyses.

Table 3. Adjusted risk ratio of breast cancer by quintile of percentage energy from fat, fat subtypes, protein, and carbohydrates, and of total energy intake among 13 707 postmenopausal women with no history of benign breast disease in the Breast Cancer Detection Demonstration Project Follow-up Cohort Study (from 1979 through 1995)

Nutrient	Quintile (Q) of intake, % energy or kcals/day					P test for trend*
	Q1	Q2	Q3	Q4	Q5	
Fat, % energy†						
No. of cases	32	53	50	59	61	
RR	1.0	1.70	1.58	1.98	2.20	.0003
95% CI		1.09–2.64	1.01–2.48	1.27–3.06	1.41–3.42	
Saturated fat, % energy†,‡						
No. of cases	35	50	58	56	56	
RR	1.0	1.24	1.31	1.21	1.24	.75
95% CI		0.80–1.93	0.83–2.07	0.75–1.96	0.75–1.96	
Unsaturated fat, % energy†,‡						
No. of cases	30	59	41	58	67	
RR	1.0	2.04	1.47	2.30	2.64	.0006
95% CI		1.29–3.22	0.89–2.44	1.40–3.78	1.56–4.44	
Oleic acid, % energy†,‡						
No. of cases	33	48	56	64	54	
RR	1.0	1.53	1.70	2.05	1.82	.03
95% CI		0.94–2.49	0.99–2.91	1.14–3.71	0.89–3.71	
Linoleic acid, % energy†,‡						
No. of cases	36	46	46	68	59	
RR	1.0	1.15	1.10	1.51	1.29	.32
95% CI		0.73–1.79	0.69–1.74	0.96–2.37	0.78–2.13	
Protein, % energy†						
No. of cases	56	48	53	56	42	
RR	1.0	0.82	0.91	0.90	0.72	.28
95% CI		0.56–2.12	0.62–1.33	0.61–1.31	0.48–1.10	
Carbohydrates, % energy†						
No. of cases	69	49	51	48	38	
RR	1.0	0.68	0.69	0.64	0.51	.002
95% CI		0.47–0.99	0.48–1.01	0.43–0.93	0.34–0.77	
Energy, kcals†,§						
No. of cases	41	47	71	55	41	
RR	1.0	1.13	1.68	1.30	0.96	.90
95% CI		0.74–1.72	1.14–2.47	0.87–1.96	0.62–1.49	

*P value (Wald test) for continuous linear term.

†Adjusted for total energy, body mass index, height, family history of breast cancer, parity, age at first birth, educational level, alcohol use, and age at menarche. RR = adjusted risk ratio; CI = confidence interval.

‡Mutually adjusted for other fat subtypes.

§Adjusted for all above factors except energy, saturated fat, and unsaturated fats.

DISCUSSION

In this large, prospective cohort study of postmenopausal women, we found little association between total fat or any

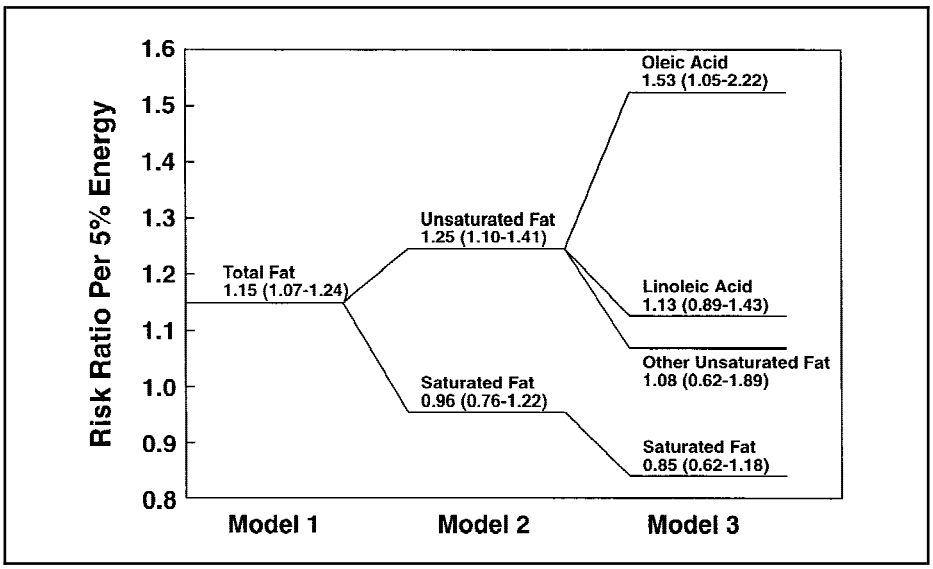

Fig. 1. Adjusted risk ratio of breast cancer associated with a five-percentage unit increase in percent energy from total fat and fat subtypes among 13 707 postmenopausal women with no history of benign breast disease participating in the Breast Cancer Detection Demonstration Project Follow-up Cohort Study (from 1979 through 1995). All models included adjustments for total energy, body mass index, height, family history of breast cancer, parity, age at first birth, educational level, alcohol intake, and age at menarche. In models 2 and 3, additional adjustments were made for other fat subtype(s).

fat subtype and breast cancer risk in the cohort as a whole. Among those women with no history of BBD, however, we found a positive association between total fat intake and breast cancer, which appeared to be attributable to unsaturated fat intake and specifically to monounsaturated fat (oleic acid).

Although women in our study were extensively screened for breast cancer and women with BBD were oversampled, we observed that other well-established risk factors for breast cancer were associated with risk *(3)*, suggesting that the etiology of breast cancer in this cohort is not atypical.

Our finding of little or no overall association between breast cancer and total fat intake is generally consistent with most other evidence from epidemiologic studies. Given the recognized high correlation between total energy and fat intake (r = .86 in our data), variations in observed risk from different studies may be, at least partially, due to the use of different methods of energy adjustment *(25,32,33)*. We examined the total fat–breast cancer risk association with use of the four methods of energy adjustment used in other studies (i.e., the standard, residual, nutrient density, and energy-partition methods) *(32,33)* and saw no evidence for an association.

Our finding of no association between any of the fat subtypes examined and breast cancer risk in the overall population is also generally consistent with other epidemiologic studies *(24)*. Only two other studies, however, adjusted for multiple fat subtypes simultaneously in their analyses. The Harvard Nurses' Health Study *(22)* also observed no association between any fat subtype and breast cancer risk. In contrast, a Swedish cohort study *(21)* reported a statistically significant protective effect for monounsaturated fat (oleic acid) and increased risk with higher polyunsaturated fat (linoleic acid) intake.

Because some dietary fat subtypes are highly correlated, it is difficult to disentangle their independent association with breast cancer. In our population, Pearson correlation coefficients with percent of calories from saturated fat were as follows: unsaturated fat, 0.64; linoleic acid, 0.30; and oleic acid, 0.82. In studies that did not simultaneously adjust for other fat subtypes, an apparent association with one type may have included the contribution of one or more other types. In studies that did simultaneously adjust, standard errors associated with risk estimates will have increased, resulting in wide CIs and a loss of precision in risk estimates.

In comparing study findings of specific fat types, it is also important to consider that the underlying foods contributing to intakes of specific fats and the chemical properties of fatty acids may differ between populations. If fatty acids are modified (e.g., hydrogenated), they may be metabolized differently and engender different breast cancer risks. The primary food that contributes to oleic acid intake in the Mediterranean, for example, is olive oil, whereas in our U.S. cohort, the primary food source was margarine. Several case–control studies *(35)* conducted in Greece, Italy, and Spain reported decreased breast cancer risks associated with increased olive oil intake (high in oleic acid). Olive oil in the Meditterranean diet, however, may also serve as a proxy for another constituent of the diet or for foods eaten in combination with a diet high in olive oil, such as fruits and vegetables *(4)*. In the United States, many margarines contain a hydrogenated form of oleic acid, which may be associated with increased breast cancer risk *(15,36)*. Thus, the breast cancer risk associated with oleic acid intake in the Meditterranean diet may well differ from that in the U.S. diet.

Our finding of an increased breast cancer risk associated with total fat, unsaturated fat, and oleic acid intake in women with no history of BBD is intriguing. Few data are available from other studies to evaluate this finding. A meta-analysis *(37)* with pooled results from seven prospective cohort studies, in contrast to our findings, reported no association between total fat intake and breast cancer risk in women with no history of BBD and a nonsignificant positive association in women with a history of BBD (RR = 1.29; 95% CI = 0.96–1.72), for a 25-g change in fat intake. To our knowledge, no previous epidemiologic studies have examined the association between fat subtypes and breast cancer in women with and without a history of BBD.

The dietary fat–breast cancer association that we observed in women with no history of BBD may be due to chance. Alternatively, we hypothesized that a real association between dietary fat and breast cancer risk may be attenuated in women with a history of BBD because of possible changes in diet, diet recall, or nondietary behaviors after diagnosis of BBD, whereas in women without a history of BBD, an association could be revealed. Consistent with this hypothesis, women with a history of BBD reported a slightly more "health promotional" dietary profile. We did not have information available to us to assess other possible changes. From a biologic perspective, dietary fat may be an important risk factor for breast cancer in women without a history of BBD, whereas for women with a

history of BBD, other factors, such as a family history of breast cancer or reproductive factors, may play a more predominant role. These explanations are conjectural and warrant further study.

Validation studies *(29,30,38–40)* have demonstrated that the food-frequency questionnaire that we used provides reasonable estimates of usual dietary intake. Also, the range of percentage of energy from each fat type in our study was consistent with national survey data for women in a similar age range *(31,41)*. Nevertheless, limitations of the food-frequency questionnaire are present and have been well described *(38,42)*. Specific fatty acids, in particular, may be subject to measurement error because of differences in fatty acid contents of multiple foods on a line item and assumptions about proportional intakes of these foods or changes in the fatty acid composition in the same foods over seasons of the year and/or in the food supply from year to year *(36,43)*. Although the measurement error present in our dietary assessment instrument could explain the lack of association that we observed between fat and breast cancer risk in the overall cohort, it is unlikely to explain the positive association that we observed in women with no history of BBD.

Similar to other epidemiologic studies conducted in the United States and in Europe, our study was also limited by the range of fat consumed by women. We did not observe a decreased breast cancer risk in women consuming less than 20% of their energy from fat, but we did not have an adequate range of intake to fully examine this association.

In summary, in this large, prospective cohort study of postmenopausal women, we found no overall association between intake of total fat or any fat subtype during adulthood and breast cancer risk. We did, however, find in women with no history of BBD a positive association between increased intake of total fat and breast cancer risk that appeared to be attributable to unsaturated fat intake. It would be valuable for this latter finding to be investigated in other studies.

REFERENCES

(1) Ursin G, Bernstein L, Pike M. Breast Cancer. In: Doll R, Fraumeni JF Jr, Muir C, editors. Trends in cancer incidence and mortality. New York (NY): Cold Spring Harbor Laboratory Press; 1994. p. 241–64.

(2) Ries L, Kosary C, Hankey B, Miller B, Clegg L, Edwards B, editors. SEER cancer statistics review, 1973–1996. Bethesda (MD): National Cancer Institute; 1999.

(3) Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer. Annu Rev Public Health 1996;17:47–67.

(4) Greenwald P. Role of dietary fat in the causation of breast cancer: point. Cancer Epidemiol Biomarkers Prev 1999;8:3–7.

(5) Hunter D. Role of dietary fat in the causation of breast cancer: counterpoint. Cancer Epidemiol Biomarkers Prev 1999;8:9–13.

(6) Buell P. Changing incidence of breast cancer in Japanese-American women. J Natl Cancer Inst 1973;51:1479–83.

(7) Carroll KK, Braden LM, Bell JA, Kalamegham R. Fat and cancer. Cancer 1986;58(8 Suppl):1818–25.

(8) Patterson RE, Haines PS, Popkin BM. Diet quality index: capturing a multidimensional behavior. J Am Diet Assoc 1994;94:57–64.

(9) Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 1993;85: 1819–27.

(10) Adelstein AM, Staszewski J, Muir CS. Cancer mortality in 1970–1972 among Polish-born migrants to England and Wales. Br J Cancer 1979;40:464–75.

(11) Prentice RL, Kakar F, Hursting S, Sheppard L, Klein R, Kushi L. Aspects of the rationale for the Women's Health Trial. J Natl Cancer Inst 1988;80:802–14.

(12) Welsch CW. Relationship between dietary fat and experimental mammary tumorigenesis: a review and critique. Cancer Res 1992;52(7 Suppl):2040s–2048s.

(13) Freedman LS, Clifford C, Messina M. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. Cancer Res 1990;50: 5710–9.

(14) Rose DP. Effects of dietary fatty acids on breast and prostate cancers: evidence from *in vitro* experiments and animal studies. Am J Clin Nutr 1997;66(6 Suppl):1513S–1522S.

(15) Ip C. Review of the effects of trans fatty acids, oleic acid, n-3 polyunsaturated fatty acids, and conjugated linoleic acid on mammary carcinogenesis in animals. Am J Clin Nutr 1997;66(6 Suppl):1523S–1529S.

(16) Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case–control studies. J Natl Cancer Inst 1990;82:561–9.

(17) Mills PK, Beeson WL, Phillips RL, Fraser GE. Dietary habits and breast cancer incidence among Seventh-day Adventists. Cancer 1989; 64:582–90.

(18) Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, et al. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. JAMA 1992;268: 2037–44.

(19) Graham S, Zielezny M, Marshall J, Priore R, Freudenheim J, Brasure J, et al. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. Am J Epidemiol 1992;136:1327–37.

(20) Hunter DJ, Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, et al. Cohort studies of fat intake and the risk of breast cancer—a pooled analysis. N Engl J Med 1996;334:356–61.

(21) Wolk A, Bergstrom R, Hunter D, Willett W, Ljung H, Holmberg L, et al. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. Arch Intern Med 1998;158:41–5.

(22) Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, Speizer FE, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999;281: 914–20.

(23) Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, et al. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study. J Natl Cancer Inst 1987;79: 465–71.

(24) Willett WC. Specific fatty acids and risks of breast and prostate cancer: dietary intake. Am J Clin Nutr 1997;66(6 Suppl):1557S–1563S.

(25) Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, et al. Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst 1992;84:1092–9.

(26) Howe GR, Friedenreich CM, Jain M, Miller AB. A cohort study of fat intake and risk of breast cancer. J Natl Cancer Inst 1991;83: 336–40.

(27) National Cancer Institute IMS Inc. and Block Dietary Data Systems. DIETSYS user's guide. Bethesda (MD): National Cancer Institute; 1994.

(28) Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.

(29) Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:58–64.

(30) Block G, Thompson FE, Hartman AM, Larkin FA, Guire KE. Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period. J Am Diet Assoc 1992;92:686–93.

(31) Block G, Subar AF. Estimates of nutrient intake from a food frequency questionnaire: the 1987 National Health Interview Survey. J Am Diet Assoc 1992;92:969–77.

(32) Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4 Suppl): 1220S–1228S; discussion 1229S–1231S.

(33) Feedman L, Kipnis V, Brown C, Schatzkin A, Wacholder S, Hartman A. Comments on "Adjustment for total energy intake in epidemiologic studies." Am J Clin Nutr 1997;65: 1229S–1231S.

(34) Sinha R, Chow W, Kulldorff M, Denobile J, Butler J, Garcia-Closas M, et al. Well-done, grilled red meat increases the risk of colorectal adenomas. Cancer Res 1999;59:4320–4.

(35) Lipworth L, Martinez ME, Angell J, Hsieh CC, Trichopoulos D. Olive oil and human cancer: an assessment of the evidence. Prev Med 1997; 26:181–90.

(36) Kohlmeier L. Biomarkers of fatty acid exposure and breast cancer risk. Am J Clin Nutr 1997;66 (6 Suppl):1548S–1556S.

(37) Hunter D, Spiegelman D, Adami HO, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Non-dietary factors as risk factors for breast cancer, and as effect modifiers of the association of fat intake and risk of breast cancer. Cancer Causes Control 1997;8: 49–56.

(38) Block G. A review of validations of dietary assessment methods. Am J Epidemiol 1982; 115:492–505.

(39) Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol 1990;43:1327–35.

(40) Mares-Perlman JA, Klein BE, Klein R, Ritter LL, Fisher MR, Fraudenheim JL. A diet history questionnaire ranks nutrient intakes in middle-aged and older men and women similarly to multiple food records. J Nutr 1993;123: 489–501.

(41) McDowell M, Briefel R, Alaimo K, et al. Energy and macronutrient intakes of persons ages 2 months and over in the United States: third National Health and Nutrition Examination Survey, Phase 1, 1988–91. Washington (DC): United States DHHS; 1994.

(42) Willett W. Reproducibility and validity of food frequency questionnaires. In: Willett W, editor. Nutritional epidemiology. New York (NY): Oxford University Press; 1998.

(43) Dwyer JT. Human studies on the effects of fatty acids on cancer: summary gaps and future research. Am J Clin Nutr 1997;66(6 Suppl): 1581S–1586S.

NOTES

Supported in part by the Cancer Prevention Fellowship Program at the National Cancer Institute, Bethesda, MD (to E. Velie).

We thank the many women who donated their time to participate in this study. In addition, we thank Jane Curtin, Leslie Carroll, and Heather Clancey of IMS Inc., Rockville, MD, for their computer support.

Manuscript received October 22, 1999; revised March 1, 2000; accepted March 14, 2000.